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# Novel erythropoiesis stimulating protein for treatment of anemia in chronic renal insufficiency

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*Background.* Novel erythropoiesis stimulating protein (NESP) is a glycoprotein with a threefold longer terminal half-life than recombinant human erythropoietin (rHuEPO) in humans. The aim of this study was to determine whether NESP is effective for the treatment of anemia at a reduced dosing frequency relative to rHuEPO in patients with chronic renal failure not yet on dialysis [chronic renal insufficiency (CRI)].

*Methods.* This was a multicenter, randomized, open-label study. A total of 166 rHuEPO-naive patients with CRI were randomized in a 3:1 ratio to receive NESP (0.45 μg/kg once weekly) or rHuEPO (50 U/kg twice weekly) administered subcutaneously for up to 24 weeks. Dose adjustments were made as necessary to achieve a hemoglobin response, defined as an increase ≥1.0 g/dL from baseline and a concentration ≥11.0 g/dL.

*Results.* During the 24-week treatment period, 93% (95% CI, 87 to 97%) of patients receiving NESP and 92% (95% CI, 78 to 98%) of patients receiving rHuEPO achieved a hemoglobin response. The median time to response was seven weeks (range of 3 to 25 weeks) in both groups. After correction of anemia, mean hemoglobin concentrations were maintained within the target range of 11.0 to 13.0 g/dL for the remainder of the 24-week treatment period. The safety profiles of NESP and rHuEPO were similar, and no antibodies were detected to either drug.

*Conclusions.* These results demonstrate that NESP safely and effectively corrects and maintains hemoglobin concentrations at a reduced dosing frequency relative to rHuEPO in patients with CRI, providing a potential benefit to patients and health care providers.

Patients with chronic renal failure (CRF) frequently experience anemia, which can significantly affect their morbidity, mortality, and quality of life. Recombinant human erythropoietin (rHuEPO) is effective for the treatment of anemia in CRF based on its ability to increase hemoglobin, virtually eliminate the need for red blood cell transfusions, mitigate symptoms associated with anemia, and improve energy and physical functioning [1, 2].

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However, in most patients, administration is required two or three times per week.

Previous research on rHuEPO has indicated that its carbohydrate content significantly affects its half-life and biological activity in vivo (abstract; Egrie, *Glycoconj J* 10:263, 1993). Novel erythropoiesis stimulating protein (NESP; ARANESP™) is a glycoprotein that was designed by introducing five amino acid changes into the primary sequence of rHuEPO to create two extra consensus N-linked glycosylation sites. Consequently, NESP has five N-linked carbohydrate chains, whereas rHuEPO has only three. The increased carbohydrate content of NESP results in a terminal half-life in humans that is approximately threefold longer than that of rHuEPO after intravenous administration (25.3 hours vs. 8.5 hours, respectively) and at least twofold longer after subcutaneous administration (48.8 hours vs. 18 to 24 hours, respectively) [3, 4]. This unique pharmacokinetic profile allows for a reduced dosing frequency, representing a potential clinical advantage over rHuEPO [5].

Preliminary studies have indicated that NESP, at a starting dose of 0.45 to 0.75 μg/kg, is safe and effective for the treatment of anemia in patients with CRF receiving dialysis [5]. However, the effects of NESP have not been evaluated in patients with CRF not yet on dialysis [chronic renal insufficiency (CRI)]. This multicenter, randomized, open-label study was designed to evaluate the efficacy and safety of NESP in this patient population. The rHuEPO treatment group was included to provide a reference reflecting current medical practice.

## METHODS

### Patients

Our study was approved by each institution's independent ethics committee, and all patients gave written informed consent before participation. Patients 18 years of age or older with a diagnosis of CRI were enrolled at 32 dialysis centers in Europe and 4 in Australia. Patients were not receiving dialysis and were rHuEPO naive (that is, had not received treatment with rHuEPO within 12 weeks before the first planned dose of study drug). Additional entry criteria included a hemoglobin concentration <11.0 g/dL, adequate iron stores (as determined by serum ferritin ≥100 μg/L), serum vitamin $B_{12}$ and folate levels above the lower limit of the normal range, and a creatinine clearance of <30 mL/min (as estimated by the Cockcroft-Gault equation). Exclusion criteria included uncontrolled hypertension (diastolic blood pressure >100 mm Hg); congestive heart failure (New York Heart Association Class III or IV); hematologic disorders that could cause anemia, systemic infection or inflammatory disease; or other disorders that could interfere with the response to NESP or rHuEPO. Patients had not received a red blood cell transfusion or androgen therapy within eight weeks of the first planned dose of study drug.

### Study design

This was a multicenter, randomized, open-label study. All patients completed a screening period within two weeks before the first dose of study drug. Eligible patients were then randomized by a centralized system to receive NESP or rHuEPO in a 3:1 ratio, respectively. NESP was administered subcutaneously at a starting dose of 0.45 μg/kg once weekly, and rHuEPO was administered subcutaneously at a starting dose of 50 U/kg twice weekly. The dose and frequency of NESP were chosen based on experience in treating anemia in dialysis patients [5]. The dose of rHuEPO was chosen to approximate the starting dose of NESP, based on a peptide mass conversion factor (1.0 μg/kg NESP = 200 U/kg rHuEPO), and the frequency of rHuEPO administration was chosen to reflect the most commonly used frequency at the participating centers. Study drug dose was adjusted by 25% of the starting dose as necessary to achieve a hemoglobin increase of ≥1.0 g/dL from baseline and to maintain hemoglobin concentrations within a range of 11.0 to 13.0 g/dL. Additionally, if a patient's hemoglobin increased by ≥2.0 g/dL during any four-week period, study drug doses were reduced by 25% of the starting dose. If a patient's hemoglobin concentration increased to >14.0 g/dL, study drug was withheld until the hemoglobin concentration fell below 12.0 g/dL and was restarted at a dose 25% lower than the previous dose. Patients received the first dose of study drug within seven days of randomization and continued treatment for 24 weeks. After 24 weeks, patients receiving NESP could continue treatment, and patients receiving rHuEPO ended the study.

The primary measure of efficacy was the proportion of patients achieving a hemoglobin response during the 24-week treatment period, defined as an increase in hemoglobin of ≥1.0 g/dL from baseline and a hemoglobin concentration of ≥11.0 g/dL. For this assessment, hemoglobin measurements were taken at two-week intervals through the end of the 24-week treatment period. The efficacy of NESP was also evaluated by assessing the time required to achieve a hemoglobin response, hemoglobin concentration over time, the dose of study drug at the time of hemoglobin response and at week 24, and the number of patients receiving red blood cell transfusions. Measurements to evaluate hemoglobin concentration over time were taken at four-week intervals (that is, at weeks 5, 9, 13, 17, 21, and 25).

Safety was assessed by monitoring adverse events, laboratory variables (hematology, biochemistry, and iron status), vital signs, and antibody formation to NESP or rHuEPO. In addition, the ability to increase hemoglobin levels safely was evaluated by the maximum increase in hemoglobin within any four-week period and the num-

ber of increases in hemoglobin ≥2.0, ≥2.5, or ≥3.0 g/dL within any four-week period. Hematology parameters and vital signs were evaluated every two weeks throughout the study. Biochemistry parameters and antibody formation were evaluated every 12 weeks, and iron status was evaluated every four weeks.

### Study medications

Novel erythropoiesis stimulating protein was supplied by Amgen Inc. (Thousand Oaks, CA, USA). Recombinant human erythropoietin (Epoetin alfa) was obtained from commercial sources and provided by the pharmacy at each study center. To ensure adequate support of the erythropoietic response to study drug, intravenous iron therapy was required to be administered to patients with serum ferritin values <100 μg/L. The intravenous iron dosing regimen used for patients with serum ferritin values <100 μg/L or ≥100 μg/L was determined by the individual center's treatment policy.

### Statistical analysis

All patients who received at least one dose of the study drug were included in the analyses of efficacy and safety. An additional, prospectively defined "per-protocol" analysis of efficacy was conducted in those patients who completed 24 weeks of treatment, had at least 75% of the postbaseline hemoglobin measurements, and received within ±25% of their total prescribed dose of study drug, no more than one incorrect dose of study drug, and no red blood cell transfusions before achieving a hemoglobin response.

Descriptive statistics were summarized for all end points according to the treatment group. This study was powered to evaluate whether a clinically meaningful proportion of patients receiving NESP achieved a hemoglobin response, which was considered to be 50% of patients, but was not designed to compare NESP and rHuEPO. The sample size of at least 120 NESP patients was chosen to give a power of >99% for demonstrating that the response rate for NESP exceeds 50% (that is, the lower limit of the confidence interval for the NESP response rate is >50%).

## RESULTS

### Patient characteristics

Patients were randomized to receive NESP (129 patients) or rHuEPO (37 patients). All 166 patients were included in the efficacy and safety analyses. The per-protocol analysis set included 105 NESP patients and 29 rHuEPO patients. Overall, 54% of patients were men, and most were white (96%). The mean age was 61 years, with a range of 19 to 87 years. Demographic characteristics were similar between the two treatment groups (Table 1). The most frequent causes of renal failure in patients receiving NESP or rHuEPO were diabetes mellitus and glomerulonephritis. Hypertension was the most common medical condition among patients in both the NESP and rHuEPO groups at baseline (91 and 84%, respectively). The mean baseline hemoglobin concentration was lower in the NESP group (9.3 g/dL, range of 6.6 to 11.0) than in the rHuEPO group (9.8 g/dL, range of 6.1 to 11.5; Table 1). Median baseline serum ferritin levels (168 and 151 μg/L in the NESP and rHuEPO groups, respectively) indicated that most patients were iron replete [6, 7]. Mean creatinine clearance was similar in the NESP (15.7 mL/min; range of 7 to 44) and rHuEPO (15.7 mL/min, range of 4 to 33) groups.

**Table 1.** Patient demographic and baseline characteristics in novel erythropoiesis stimulating protein (NESP)- or recombinant human erythropoietin (rHuEP)-treated patients[a]

| | NESP ($N$ = 129) | rHuEPO ($N$ = 37) |
|---|---|---|
| Sex | | |
| Men | 70 (54%) | 19 (51%) |
| Women | 59 (46%) | 18 (49%) |
| Race | | |
| Asian | 3 (2%) | 1 (3%) |
| Black | 3 (2%) | 0 (0%) |
| White | 123 (95%) | 36 (97%) |
| Age *years*[b] | 60.4 (15.0) | 60.6 (15.7) |
| Primary cause of renal failure | | |
| Diabetes | 32 (25%) | 8 (22%) |
| Hypertension | 15 (12%) | 1 (3%) |
| Glomerulonephritis | 24 (19%) | 10 (27%) |
| Polycystic kidney disease | 6 (5%) | 2 (5%) |
| Other urologic | 5 (4%) | 0 (0%) |
| Other | 32 (25%) | 11 (30%) |
| Unknown | 15 (12%) | 5 (14%) |
| Hemoglobin *g/dL*[b] | 9.3 (1.0) | 9.8 (1.1) |
| Serum ferritin *μg/L*[c] | 168 (30–1420) | 151 (31–899) |
| Creatinine clearance *mL/min*[b] | 15.7 (6.6) | 15.7 (6.4) |

[a] Baseline is defined as the closest measurement taken before the first dose of study drug
[b] Mean (SD)
[c] Median (range)

### Efficacy

A hemoglobin response (defined as an increase of ≥1.0 g/dL from baseline and a concentration ≥11.0 g/dL) was achieved by 93% (95% CI, 87 to 97%) of patients receiving NESP during the 24-week treatment period. Similarly, 92% (95% CI, 78 to 98%) of patients achieved a response in the rHuEPO group. These findings were supported by the per-protocol analysis, in which 94% of the NESP patients (95% CI, 88 to 98%) and 100% of the rHuEPO patients (95% CI, 88 to 100%) achieved a hemoglobin response. The percentage of patients achieving a hemoglobin increase of ≥1.0 g/dL from baseline also was comparable between the NESP (99%; 95% CI, 96 to 100%) and rHuEPO (95%; 95% CI, 82 to 99%) groups. In both treatment groups, the median time to

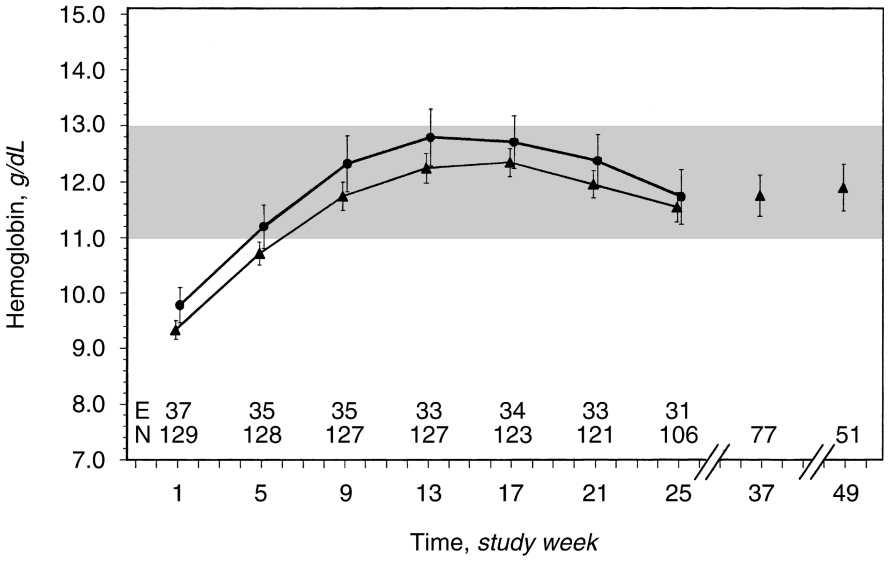


**Fig. 1. Mean (95% CI) hemoglobin concentrations at four-week intervals.** The shaded area indicates target range. Symbols are the patients receiving: (●) recombinant human erythropoietin (rHuEPO); (▲) novel erythropoiesis stimulating protein (NESP). Abbreviations are: E, number of patients receiving rHuEPO; N, number of patients receiving NESP.

achieve a hemoglobin response was seven weeks (range of 3 to 25 weeks).

Mean hemoglobin concentrations increased over the initial 12 weeks for patients in both groups and were maintained within the target range of 11.0 to 13.0 g/dL for the remainder of the 24-week treatment period. In patients continuing to receive NESP after the 24-week treatment period, the mean hemoglobin concentration remained within the target range for up to 48 weeks (Fig. 1). The difference in hemoglobin levels observed between the NESP and rHuEPO patients at baseline appeared to remain constant throughout the study; thus, no difference in the change in hemoglobin from baseline between the two treatment groups was evident. After the initial four weeks of treatment, the two groups had comparable increases in mean hemoglobin concentrations: 1.38 g/dL (95% CI, 1.21 to 1.55) in the NESP group and 1.40 g/dL (95% CI, 1.07 to 1.72) in the rHuEPO group. Mean changes in hemoglobin from baseline were very similar between the treatment groups up to 24 weeks.

Fifty-eight percent of NESP patients and 59% of rHuEPO patients did not require any dose adjustment before achieving a hemoglobin response. A similar percentage of patients receiving NESP or rHuEPO had a dose increase (35 and 32%, respectively) or a dose decrease (7 and 9%, respectively) before achieving a hemoglobin response. At the time of hemoglobin response, the median weekly weight-adjusted dose of NESP was 0.46 μg/kg (range of 0.3 to 2.3 μg/kg), and the corresponding dose of rHuEPO was 100 U/kg (range of 75 to 175 U/kg). Both doses were nearly identical to those at the beginning of the study. At week 24, median study drug doses had decreased to 0.34 μg/kg (range of 0.0 to 1.3 μg/kg) in patients receiving NESP and to 56.9 U/kg (range of 19 to 250 U/kg) in patients receiving rHuEPO. The percentage of patients with dose reductions to levels below their starting dose up to week 24 was similar in the NESP (68%) and rHuEPO (70%) groups. In patients who continued to receive NESP after the 24-week treatment period, the median weekly weight-adjusted dose at week 48 was 0.30 μg/kg (range of 0.1 to 1.7).

Few patients required a red blood cell transfusion in the NESP or rHuEPO treatment groups (5 and 8%, respectively). Only three NESP-treated patients and two rHuEPO-treated patients received a red blood cell transfusion before achieving a hemoglobin response.

## Safety

The safety profiles of NESP and rHuEPO were similar. A total of 107 of 129 NESP patients (83%) and 24 of 37 rHuEPO patients (65%) experienced at least one adverse event during the study, most of which were mild to moderate in severity. The interpretation of differences between the treatment groups is confounded by the open-label design of the study and the potential overattribution of adverse events to a novel agent (NESP) compared with an established therapy. Adverse events occurring in more than 10% of patients in either treatment group are presented in Table 2. The most frequently reported adverse events in the NESP and rHuEPO groups were hypertension (32 and 22%, respectively) and peripheral edema (13 and 11%, respectively). Most of these events were attributed to concurrent medical conditions and were consistent with events expected in this patient population. Adverse events that were considered by the investigator to be treatment related were reported with the same frequency in each treatment group (30% NESP and 27% rHuEPO). Hypertension was the most common of these events (21% NESP and 19% rHuEPO).

There were six reported deaths (4% NESP and 3%

**Table 2.** Adverse events occurring in >10% of novel erythropoiesis stimulating protein (NESP)- or recombinant human erythropoietin (rHuEPO)-treated patients[a]

| Adverse event | NESP ($N$ = 129) | rHuEPO ($N$ = 37) |
|---|---|---|
| Hypertension | 41 (32%) | 8 (22%) |
| Peripheral edema | 17 (13%) | 4 (11%) |
| Fatigue | 16 (12%) | 0 (0%) |
| Diarrhea | 14 (11%) | 3 (8%) |
| Headache | 14 (11%) | 4 (11%) |
| Nausea | 11 (9%) | 5 (14%) |
| Pruritis | 7 (5%) | 4 (11%) |

[a] Data are presented as the number of patients (%) experiencing each adverse event.

**Table 3.** Deaths during the study or within 28 days after withdrawal in novel erythropoiesis stimulating protein (NESP)- or recombinant human erythropoietin (rHuEPO)-treated patients

| Treatment group | Age/sex | Study week | Primary cause of death |
|---|---|---|---|
| rHuEPO | 75/M | 7 | Cardiac arrest |
| NESP | 64/M | 16 | Cardiac arrest |
| NESP | 75/F | 13[a] | Cachexia |
| NESP | 53/M | 10[a] | Multi-organ failure |
| NESP | 64/M | 22 | Cardiac arrest |
| NESP | 64/F | 23 | Hematemesis |

[a] Occurred within 28 days after withdrawal from the study

rHuEPO) during the 24-week treatment period or within 28 days after withdrawal from the study (Table 3). The deaths were largely due to cardiovascular failure and occurred in patients with a history of cardiovascular disease.

Increases in hemoglobin were well controlled in patients receiving NESP or rHuEPO. The mean of the maximum increase in hemoglobin over any four-week interval was 1.99 g/dL (95% CI, 1.88 to 2.11) in the NESP group and 2.13 g/dL (95% CI, 1.88 to 2.39) in the rHuEPO group. The percentage of patients with a hemoglobin increase of ≥2.0 g/dL over any four-week interval was 51% in the NESP group and 60% in the rHuEPO group. In addition, a lower percentage of patients in the NESP group relative to the rHuEPO group had a hemoglobin increase of ≥2.5 g/dL (21 and 32%, respectively) or ≥3.0 g/dL (9 and 14%, respectively) over any four-week period. In patients who had study drug withheld for hemoglobin concentrations >14.0 g/dL (24% NESP and 35% rHuEPO), the median time required for hemoglobin levels to return to ≤12.0 g/dL was similar in the NESP (7 weeks, range of 2 to 13) and rHuEPO (9 weeks, range of 6 to 13) groups (Fig. 2).

After four weeks of treatment, median serum ferritin concentrations had decreased in the NESP and rHuEPO groups from baseline values of 168 and 151 μg/L to 80 and 63 μg/L, respectively. Median serum ferritin concentrations remained <100 μg/L until week 17, when values increased to 108 and 101 μg/L in the NESP and rHuEPO groups, respectively. Median concentrations remained above 100 μg/L for the rest of the 24-week treatment period. Intravenous iron was administered to 77% of patients receiving NESP and 81% of patients receiving rHuEPO, at a total mean patient dose of 685 mg and 678 mg, respectively. In addition, oral iron was administered to a similar proportion of patients in the NESP (52%) and rHuEPO (51%) groups.

Vital signs were stable during the 24-week treatment period in both treatment groups. In patients receiving NESP, mean ± SD systolic and diastolic blood pressure values were 155 ± 19 and 81 ± 11 mm Hg, respectively, at baseline and 146 ± 20 and 79 ± 12 mm Hg, respectively, at week 25. In the rHuEPO group, values were 141 ± 21 and 79 ± 10 mm Hg at baseline and 143 ± 23 and 79 ± 8 mm Hg at week 25.

No clinically meaningful changes in laboratory values were evident, and values were similar between the NESP and rHuEPO groups. Mean ± SD creatinine clearance values were 15.7 ± 6.6 mL/min in the NESP group and 15.7 ± 6.4 mL/min in the rHuEPO group at baseline, and 14.1 ± 6.7 mL/min and 13.7 ± 7.6 mL/min, respectively, after 24 weeks of treatment. No antibody formation to NESP or rHuEPO was detected for any patient during the study.

## DISCUSSION

In patients with chronic renal failure, anemia is associated with an increased risk of cardiovascular morbidity and mortality and a reduction in quality of life. Correction of hemoglobin and hematocrit levels has been shown to reduce cardiovascular risk factors such as left ventricular hypertrophy and improve energy and physical functioning, emphasizing the importance of treating anemia in this population [2, 8, 9].

This is the first report of the administration of NESP to patients with CRI. The results of this study demonstrate that NESP, administered once weekly at a starting dose of 0.45 μg/kg, is safe and effective for the correction of anemia and maintenance of hemoglobin concentrations in this patient population. Of the 129 patients randomized to receive NESP, 93% achieved a hemoglobin response during the 24-week treatment period. Although hemoglobin concentrations were lower in the NESP group than in the rHuEPO group at baseline, both the proportion of patients achieving a hemoglobin response and the time to achieve this response were the same for patients receiving NESP once weekly or rHuEPO administered twice weekly. The degree of anemia correction with NESP treatment was also similar to that observed in previous studies of rHuEPO administered three times weekly in patients with CRI [10–12].

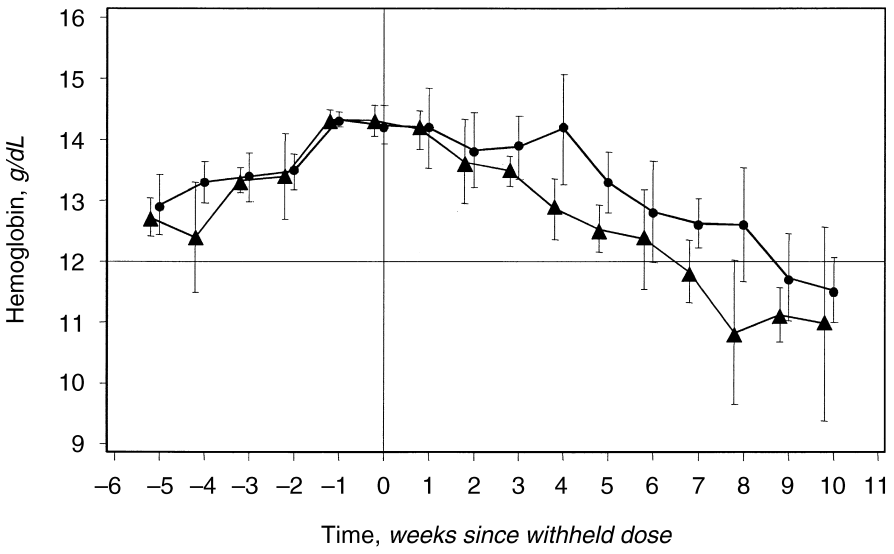


**Fig. 2. Time required for hemoglobin concentrations to return to ≤12.0 g/dL after withheld doses for hemoglobin concentrations >14.0 g/dL.** Symbols are: (●) rHuEPO ($N$ = 13); (▲) NESP ($N$ = 31). Means and 95% CIs are shown.

Consistent with previous observations of NESP administered intravenously or SC in patients with CRF receiving dialysis [5], a NESP starting dose of 0.45 μg/kg/week was effective for the correction of anemia in the CRI population. The median dose of NESP at the time patients achieved the target hemoglobin range was similar to the starting dose. However, the median NESP dose was reduced to 0.34 μg/kg after 24 weeks of treatment, potentially reflecting titration to maintain hemoglobin within the target range. Reduced maintenance doses were also observed for patients receiving rHuEPO in this study and have been reported in other studies of patients with CRF receiving rHuEPO [1, 13].

Adverse events were consistent with those expected in a population of patients with CRI and were generally considered unrelated to the study drug. While a higher overall incidence of adverse events was reported for the NESP group than for the rHuEPO group, this difference may have been a consequence of the open-label design of the study and the potential over-attribution of adverse events to a novel agent compared to an established therapy. The 3:1 randomization of patients to NESP or rHuEPO and the resulting small number of patients evaluated in the rHuEPO group may have also contributed to the observed difference. Patients in the NESP group had lower baseline hemoglobin, a higher incidence of hypertension at baseline (91% NESP and 84% rHuEPO), and higher baseline systolic blood pressure values (155 mm Hg NESP and 141 mm Hg rHuEPO). These results suggest that the NESP group had a greater burden of comorbidity and may partially explain the difference in adverse events between treatment groups, particularly since hypertension was the most common adverse event reported in this study.

No clinically significant changes were observed for any laboratory or vital sign measures, and changes in mean creatinine clearance were similar between treatment groups.

The correction of anemia with NESP treatment was well controlled, with mean hemoglobin concentrations maintained within the target range of 11.0 to 13.0 g/dL for up to 48 weeks. During the initial 24-week treatment phase, increases in hemoglobin over any four-week period were <2.5 g/dL in most patients, consistent with current recommendations for the management of anemia in CRI [6, 7]. In patients who had doses withheld for hemoglobin concentrations >14.0 g/dL during the study, the time required for levels to return to ≤12.0 g/dL was similar in the NESP and rHuEPO treatment groups. This result suggests that the rate of decline in hemoglobin after withholding NESP or rHuEPO therapy is primarily determined by destruction of circulating red blood cells as they reach the end of their lifespan, and not by clearance of the study drug.

Median serum ferritin concentrations in both treatment groups decreased below the recommended level of 100 μg/L [6, 7] during the initial correction of anemia and subsequently increased following supplemental intravenous iron therapy. Other studies in patients with CRI receiving rHuEPO therapy have also reported a high incidence of absolute or functional iron deficiency requiring intravenous or oral supplementation [10, 11, 14]. As iron deficiency is the most common cause of resistance to rHuEPO therapy, iron stores should be monitored regularly in patients receiving NESP to ensure adequate support of the erythropoietic response. Further research into optimal iron supplementation in this population is warranted.

Although rHuEPO most commonly is administered two or three times weekly for the treatment of anemia

in CRF, it has also been used once weekly in some patients. As a result of the extended half-life of NESP relative to rHuEPO, even longer dosing intervals are possible with NESP therapy [3]. In a randomized, comparative study of NESP and rHuEPO in dialysis patients, 95% of patients who were receiving rHuEPO once weekly at baseline successfully maintained stable hemoglobin concentrations when switched to NESP administered once every two weeks [5]. The longer dosing interval with NESP offers the possibility of greater convenience and less patient discomfort by reducing the number of physician office visits (where standard practice) and subcutaneous injections. With dose administration once weekly or once every two weeks, patients can avoid up to 104 injections per year. Further clinical studies to evaluate the efficacy and safety of NESP at extended dosing intervals are currently underway.

In conclusion, these results demonstrate that NESP safely and effectively corrects and maintains hemoglobin concentrations at a reduced dosing frequency relative to rHuEPO in patients with CRI, providing a potential benefit to patients and health care providers.

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